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<p>(21) International Application Number: PCT/GB95/02843 (22) International Filing Date: 5 December 1995 (05.12.95) (71) Applicant (for all designated States except US): ADCOCK IN-GRAM LIMITED [ZA/ZA]; 209 15th Road, Randjiespark, Midrand 1685 (ZA). (72) Inventors; and (75) Inventors/Applicants (for US only): JOOSTE, Henri [ZA/ZA]; 86 Cydonia Road, Wychwood, Johannesburg 2001 (ZA). MITCHELL, Duncan [ZA/ZA]; 73A Fourth Street, Linden, Johannesburg 2001 (ZA). CARTMELL, Steven, Myles [GB/ZA]; 10 Opperman Street, Jan Cilliers Park, Welkom 9459 (ZA). (74) Agents: TOWLER, Philip, Dean et al.; Frank B. Dehn & Co., 179 Queen Victoria Street, London EC4V 4EL (GB).</p>		<p>(81) Designated States: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING A SKELETAL MUSCLE RELAXANT, A NON-STEROIDAL ANTIINFLAMMATORY AGENT AND AN ANALGESIC</p> <p>(57) Abstract</p> <p>A pharmaceutical composition comprises, as active ingredients: a skeletal muscle relaxant, particularly baclofen; a non-steroidal anti-inflammatory agent selected from propionic acid derivatives, acetic acid derivatives, fenamic acid derivatives, biphenylcarboxylic acid derivatives, oxicams and pharmaceutically acceptable salts thereof, particularly ibuprofen; and an analgesic, preferably selected from paracetamol, codeine, pharmaceutically acceptable salts thereof and mixtures thereof. The composition has muscle relaxant anti-inflammatory and antinociceptive activity and may be used in the treatment of skeletal muscle disorders in mammals, and more particularly the treatment of muscle pain, especially that resulting from spasticity or trauma. The composition has been found to have enhanced activity against pain generally and to have activity against pain associated with ischaemia.</p>		

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PHARMACEUTICAL COMPOSITION COMPRISING A SKELETAL MUSCLE RELAXANT, A NON-STEROIDAL ANTIINFLAMMATORY AGENT AND AN ANALGESIC

BACKGROUND OF THE INVENTION

This invention relates to a pharmaceutical composition.

Centrally acting skeletal muscle relaxants are generally prescribed either as single agents or as components of combination products. As combination products, the skeletal muscle relaxant may be combined with an analgesic such as acetaminophen or aspirin. It is also known to combine the skeletal muscle relaxant with a combination of aspirin and caffeine.

WO 8603681 describes and claims a pharmaceutical composition for use in the treatment of a skeletal muscle disorder in a mammal comprising an effective amount of a skeletal muscle relaxant and an analgesically effective amount of a non-steroidal anti-inflammatory drug such as ibuprofen, naproxen or diclophenac. Caffeine can optionally be included in the composition.

SUMMARY OF THE INVENTION

A pharmaceutical composition according to the invention comprises, as active ingredients:

a skeletal muscle relaxant;

a non-steroidal anti-inflammatory agent selected from propionic acid derivatives, acetic acid derivatives, fenamic acid derivatives, biphenylcarboxylic acid derivatives, oxicams and pharmaceutically acceptable salts thereof; and

an analgesic, preferably selected from paracetamol, codeine, pharmaceutically acceptable salts thereof and mixtures thereof.

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The composition of the invention has useful properties in the treatment of humans and animals:

The composition of the invention has muscle-relaxant, anti-inflammatory and antinociceptive activity and may be used in the treatment of skeletal muscle disorders and more particularly for the treatment of muscle pain, especially that resulting from spasticity or trauma.

Further, the composition of the invention has surprisingly been found to have enhanced activity against pain generally and to have activity against pain associated with ischaemia.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1: Change in tail flick latency (mean \pm SEM, n=10) following intraperitoneal administration of baclofen 0,18 mg/kg and paracetamol 18 mg/kg + ibuprofen 14 mg/kg + baclofen 0,18 mg/kg.

Figure 2: Change in tail flick latency (mean \pm SEM, n=10) during reperfusion of the tail, from the value measured in the same animal before application of the tourniquet, following IP treatment with saline and baclofen. Asterisks signify values significantly different from those measured in saline-treated animals.

Figure 3: Index of antihyperalgesia of three doses of baclofen, calculated using changes in tail flick latency evident following 30 min reperfusion (see Figure 2). The index of

antihyperalgesia was calculated using the following formula:

$$INDEX = \frac{(TFL_{post} - TFL_{pre})_S - (TFL_{post} - TFL_{pre})_A}{(TFL_{post} - TFL_{pre})_S} \times 100$$

where TFL_{post} = reperfusion tail flick latency (s); TFL_{pre} = tail flick latency (s) before application of the tourniquet, S = saline; A = agent.

An index of antihyperalgesia of zero corresponds to no significant antihyperalgesic activity; a value of 100% corresponds to complete abolition of hyperalgesia. A regression equation of the form $y = a + bx^c$ was fitted. The ED_{50} of baclofen calculated from the equation, is 0,22 mg/kg.

Figure 4: Index of antihyperalgesia (mean \pm SEM, n=10) calculated at 30 min of reperfusion for baclofen 0,18 mg/kg, baclofen 0,18 mg/kg plus ibuprofen 14 mg/kg, and various combinations of baclofen with paracetamol and ibuprofen.

Figure 5: Addition of the index of antihyperalgesia at 30 min of reperfusion for baclofen 0,18 mg/kg alone plus paracetamol 18 mg/kg + ibuprofen 14 mg/kg alone compared to the index of antihyperalgesia of all three agents administered together.

Figure 6: Rotarod performance, expressed as a percentage of the performance of animals receiving the vehicle. The asterisk signifies a value significantly different from control ($p < 0,001$, Wilcoxon signed rank test).

DESCRIPTION OF EMBODIMENTS

The pharmaceutical composition of the invention may provide each of the active ingredients in therapeutically effective amounts. Thus, in such a case, the skeletal muscle relaxant will be provided in an amount sufficient to produce a muscle relaxing effect, the non-steroidal anti-inflammatory agent will be present in an amount sufficient to produce an anti-inflammatory effect; and the analgesic will be present in an amount sufficient to produce an analgesic effect.

One or more of the active ingredients may also be provided in a sub-therapeutic amount.

The pharmaceutical composition of the invention is preferably provided in the form of dosage units with each unit containing all of the active ingredients. The dosage units may be capsules, tablets or syrups and will be provided with usual excipients and carriers.

Examples of suitable skeletal muscle relaxants are analexin, baclofen, chlormezanone, cyclobenzaprine, orphenadrine, dantrolene, chlorzoxazone, methocarbamol and pharmaceutically acceptable salts thereof.

Examples of suitable non-steroidal anti-inflammatory agents are ibuprofen, naproxen, ketoprofen, tiaprofenic acid, diclofenac, indomethacin, sulindac, mefenamic acid, piroxicam, sudoxicam and pharmaceutically acceptable salts thereof.

In a preferred form of the invention, the composition comprises ibuprofen with baclofen and either paracetamol or codeine or a mixture of paracetamol and codeine.

Examples of the invention are described hereinafter.

TABLETS		
Ibuprofen	100-600mg	100-600mg
Baclofen	0,5-150mg	0,5-150mg
Paracetamol	-	100-600mg
Codeine Phosphate	5-60mg	-
Binders	0,2-30% m/m	0,2-30% m/m
Diluents	10-90% m/m	10-90% m/m
Disintegrants	0,1-20% m/m	0,1-20% m/m
Lubricants	0,1-10% m/m	0,1-10% m/m

CAPSULES		
Ibuprofen	100-600mg	100-600mg
Baclofen	0,5-150mg	0,5-150mg
Paracetamol	-	100-600mg
Codeine Phosphate	5-60mg	-
Binders	0-20% m/m	0-20% m/m
Diluents	10-90% m/m	10-90% m/m
Disintegrants	0,1-10% m/m	0,1-10% m/m
Lubricants	0-20% m/m	0-20% m/m

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The amounts specified above can be provided in a single or multiple tablets or capsules.

SUSPENSION	5 - 10ml	5 - 10ml
Ibuprofen	100-600mg	100-600mg
Baclofen	0,5-150mg	0,5-150mg
Paracetamol	-	100-600mg
Codeine Phosphate	5-60mg	-
Solvents, solubilizers stabilizers	1-95% m/m	1-95% m/m
Colouring agents	0-0,5% m/m	0-0,5% m/m
Preservatives/anti- oxidants	0,05-4% m/m	0,05-4% m/m
Flavourants	0,01-5% m/m	0,01-5% m/m

The antinociceptive activity of a combination of paracetamol, ibuprofen and baclofen administered parentally in rats was investigated. The methods used in the investigation are set out hereinafter.

METHODS

Animals

Male Sprague-Dawley rats (*Rattus norvegicus*) weighing 250-275g were used for nociceptive tests. The rats were housed in groups of five per cage at an ambient temperature of 21-23°C, on a 12-hour light, 12-hour dark cycle and were allowed free access to standard rat chow and tap water. Groups of ten rats were used to test each agent at each dose.

The activity of the putative antinociceptive agents against noxious thermal stimuli (using a modified tail flick test), against noxious ischaemia, and against reperfusion hyperalgesia were investigated.

The rat's tail was submerged in a water bath controlled at 49°C, and the time to the first co-ordinated motor response of the tail measured, with a safety cut-off at 30s. Before and between measurements, tail skin temperature was maintained at 29°C by placing all but the proximal 20mm of the tail in another temperature controlled bath, to obviate the potential confounding effects of changes in tail temperature on tail flick latency.

To measure the response to a noxious ischaemic stimulus, an inflatable tourniquet was applied to the base of the restrained rat's tail. The moment the rats exhibited an escape response, the tourniquet was deflated. The time between application of the tourniquet and the escape response was recorded as the escape latency. To prevent tissue damage, the tourniquet was removed if the rat had not responded within 30 minutes.

The measurement of hyperalgesia followed on measurement of escape latency. During the period of reperfusion which followed the release of the tourniquet mentioned above, tail flick latency was measured again, and compared the value with that measured in the same animal before application of the tourniquet. Reperfusion hyperalgesia is manifest as a reduced tail flick latency during reperfusion.

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Control experiments were performed by placing a sham tourniquet on the tail for 12 minutes; this time is equal to the mean escape latency measured in previous experiments.

Rats were habituated to restrainers for three hours per day on two consecutive days before any measurements were made. On experimental days, the animals were placed in restrainers 15 minutes before any testing. Experiments were carried out between 09:00 and 13:00 at an ambient temperature of 24°C. At least 48 hours were allowed between successive measurements on individual animals.

Tail flick latency was measured (mean of three measurements, 1 minute apart) and then the agent under test administered. Half an hour later the tourniquet was applied and escape latency measured. Immediately after release of the tourniquet, tail flick latency was measured again, and the measurements repeated at 0,5 hour intervals for 2 hours of reperfusion. The test battery lasted between 160 and 195 minutes following injection of the agent.

Test of motor function.

To test whether baclofen alone or in combination with paracetamol and ibuprofen had any effect on motor function, a modification of the rotarod technique was used, which measures the length of time an animal can remain on a rotating rod. Selection and training procedures were used to attain consistent rotarod performances over extended periods. Twenty young rats were selected for their ability to perform on the rotarod and trained for 30 minutes a day over a 14-day period at increasing speeds.

To test potential effects of the test agents on motor function, the rats were divided into groups of ten animals each and, on successive days, given either saline, benzyl alcohol, baclofen 0,18 and 0,45 mg/kg, or the combination of baclofen 0,18 mg/kg + paracetamol 18 mg/kg + ibuprofen 14 mg/kg in random order. Each animal therefore served as its own control. The agent or vehicle was administered 30 minutes before rotarod testing. The time from the onset of running until falling off the rod served as each rat's performance time. The speed of the rotarod was 25 rpm and the maximum running time was set at 60 minutes.

Agents

Baclofen was dissolved in physiological saline (0,9% m/v NaCl) and paracetamol and ibuprofen were dissolved in 4% m/v/benzyl alcohol; the agents were administered intraperitoneally in 0,25 ml boluses. Baclofen was administered on its own at doses of 0,05, 0,18 and 0,45 mg/kg. A combination of baclofen with paracetamol and ibuprofen then was administered at various doses.

Statistics.

The student's test with Benferroni correction for multiple comparisons and the one-way analysis of variance were used for analysis of data on nociception. The Wilcoxon signed ranked test was used for analysis of rotarod data.

Ethical considerations

The experimental procedures were approved by the Animal Ethics Committee of the University of the Witwatersrand (Certificate No. 94/113/4) and complied with the recommendations of the Committee for Research and Ethical Issues of the International Association for the Study of pain.

RESULTS

Figure 1 shows the effects of the agents on tail flick latency in the absence of a conditioning stimulus. There was no change in tail flick latency, compared to that prevailing in the same animal before administration of the agents, at any of the time intervals tested, for baclofen 0,18 mg/kg or for baclofen 0,18 mg/kg + paracetamol 18 mg/kg + ibuprofen 14 mg/kg. At the doses tested, in the absence of a conditioning stimulus, baclofen on its own or in combination with paracetamol and ibuprofen therefore had no antinociceptive action against noxious thermal stimulation.

The escape latencies to the noxious ischaemic stimulus following administration of saline, benzyl alcohol 4% m/v and of the highest dose of the putative antinociceptive agents are shown in Table 1. At the doses tested, none of the agents affected the rats' responses to the noxious ischaemic stimulus (one-way ANOVA $F=0,23$, $p>0,05$).

Table 1: Escape latencies (mean \pm SEM) to a noxious ischaemic stimulus, following intraperitoneal administration 30 minutes previously of the agents, at the highest doses tested.

Agent	Escape latency (min)	n
Saline 0,25ml	16,3 \pm 1,4	20
Benzyl alcohol 0,25ml	19,9 \pm 2,5	10
Baclofen 0,45mg/kg	19,1 \pm 2,4	10
Paracetamol 18mg/kg & Ibuprofen 14mg/kg	18,1 \pm 2,7	10
Paracetamol 18mg/kg Ibuprofen 14mg/kg & Baclofen 0,18mg/kg	18,1 \pm 2,7	10

Evidence that baclofen exhibited antinociceptive activity is provided in Figure 2, which shows the change in tail flick latency during tail reperfusion, following earlier administration of saline and baclofen. During reperfusion of the tail there was a significant decrease in tail flick latency following administration of saline and baclofen 0,05 and 0,18 mg/kg, that is there was reperfusion hyperalgesia. Baclofen 0,45 mg/kg abolished the hyperalgesia evident in saline-treated animals.

Figure 3 shows some of the results of Figure 2 expressed in a different way. The changes in tail flick latency measured at 30 minutes of reperfusion of the tail are expressed as an index of antihyperalgesia. The ED₅₀ of baclofen was 0,22 mg/kg.

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Figure 4 shows the indices of antihyperalgesia calculated from the change in tail flick latency at 30 minutes of reperfusion of the tail for baclofen 0,18 mg/kg on its own, paracetamol 18 mg/kg + ibuprofen 14 mg/kg, and the other dose combinations of all three agents which were administered. The only dose of the combination, amongst those we tested, which significantly attenuated reperfusion hyperalgesia was the baclofen 0,18 mg/kg + paracetamol 18 mg/kg and ibuprofen 14 mg/kg.

Figure 5 shows the indices of antihyperalgesia of baclofen 0,18 mg/kg on its own, 18 mg/kg + ibuprofen 14 mg/kg, and the combination of all three agents at these doses. The index of antihyperalgesia for the three agents administered in combination was 83%, whilst addition of the indices of antihyperalgesia of the individual components (baclofen 0,18 mg/kg, 37% and paracetamol 18 mg/kg + ibuprofen 14 mg/kg, 20%) amounted to 57%. Combining baclofen with ibuprofen and paracetamol therefore enhanced the antihyperalgesic effect of baclofen.

The effect on rotarod performance of baclofen 0,18 and 0,45 mg/kg as well as that of the combination baclofen 0,18 mg/kg + paracetamol 18 mg/kg + ibuprofen 14 mg/kg is shown in Figure 6. Baclofen 0,45 mg/kg caused a significant decrement in rotarod performance, but baclofen 0,18 mg/kg in combination with paracetamol 18 mg/kg and ibuprofen 14 mg/kg did not affect rotarod performance significantly.

CONCLUSIONS

1. The test has shown that baclofen is a potent antihyperalgesic agent, in the hyperalgesic state induced by reperfusion of previously

ischaemic tissue. Such antihyperalgesia is typical of non-steroidal anti-inflammatory drugs, and the potency of baclofen is considerably greater than that of indomethacin, the most potent non-steroidal anti-inflammatory tested in this assay of antihyperalgesia. The high potency of baclofen, as an antihyperalgesic agent, does not derive from its ability to relax muscle. Although baclofen, at the highest dose tested, impaired motor co-ordination in the rats, it did not affect tail flick latency in the absence of a conditioning stimulus, so that the tail flick mechanism, which depends on proper muscle function, was intact throughout the assay.

2. Opiates typically attenuate the responses of rats to noxious thermal and ischaemic stimuli, even in the absence of a conditioning stimulus inducing hyperalgesia. At the doses investigated, neither baclofen alone nor baclofen in combination with paracetamol and ibuprofen showed evidence of this opiate-like antinociception. However, following the induction of the state of hyperalgesia, baclofen, at the highest dose tested, not only reversed the hyperalgesia but also appeared to desensitise the animals to noxious thermal stimuli. Thus, the changes in the nociceptive system following a conditioning stimulus may not only induce hyperalgesia, but may also allow agents to express analgesic activity in addition to antihyperalgesic activity.
3. The test has shown that, at the highest dose of baclofen which has no effect on motor function in rats, the antinociceptive activity of baclofen is enhanced by the addition of paracetamol and ibuprofen. Combining baclofen with paracetamol and ibuprofen produced an

agent with strong antinociceptive action, at doses at which neither baclofen alone nor the paracetamol and ibuprofen combined had any detectable antinociceptive action.

4. A combination of baclofen with ibuprofen and paracetamol, at the doses currently registered for human use (e.g. 5mg baclofen + 200mg ibuprofen + 250mg paracetamol, in a single capsule) should have muscle relaxant, anti-inflammatory and antinociceptive activity. That suite of activities makes the combination highly attractive for the treatment of muscle pain, especially that resulting from spasticity or trauma. Based on the experiments in rats, there is no reason to believe that combining baclofen with paracetamol and ibuprofen would enhance the adverse effects of any of these agents.
5. The synergy makes it possible to construct, for human use, a low-dose combination of baclofen, ibuprofen and paracetamol composition with significant antinociceptive function, but with appreciably fewer side effects than those of the conventional doses of either baclofen or ibuprofen and paracetamol.
6. Although the combination of baclofen with ibuprofen and paracetamol may be used as an agent for treating muscle pain, the antinociceptive activity of baclofen, either alone or in combination with cyclo-oxygenase inhibitors, does not appear to be confined to pain of muscular origin. Indeed, in the above tests on rats, no muscle pain was involved. The combination should be effective in hyperalgesia of any origin.

CLAIMS

1.

A pharmaceutical composition comprising, as active ingredients:

a skeletal muscle relaxant;

a non-steroidal anti-inflammatory agent selected from propionic acid derivatives, acetic acid derivatives, fenamic acid derivatives, biphenylcarboxylic acid derivatives, oxicams and pharmaceutically acceptable salts thereof; and

an analgesic.

2.

A pharmaceutical composition according to claim 1 which is provided in the form of dosage units with each unit containing each of the active ingredients.

3.

A pharmaceutical composition according to claim 1 or claim 2 wherein the skeletal muscle relaxant is selected from analexin, baclofen, chlormexanone, cyclobenzaprine, orphenadrine citrate, dantrolene, chlorzoxazone, methocarbamol and pharmaceutically acceptable salts thereof.

4.

A pharmaceutical composition according to any one of the preceding claims wherein the non-steroidal anti-inflammatory agent is selected from ibuprofen, naproxen, ketoprofen, tiaprofenic acid, diclofenac, indomethacin, sulindac, mefenamic acid, piroxicam, sudoxicam, and pharmaceutically acceptable salts thereof.

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5.

A pharmaceutical composition according to any one of the preceding claims wherein the analgesic is selected from paracetamol, codeine and pharmaceutically acceptable salts thereof and mixtures thereof.

6.

A pharmaceutical composition according to any one of the preceding claims which comprises ibuprofen, baclofen and paracetamol as the active ingredients.

7.

A pharmaceutical composition according to any one of claims 1 to 5 which comprises ibuprofen, baclofen and codeine as the active ingredients.

8.

A pharmaceutical composition according to any one of claims 1 to 5 which comprises ibuprofen, baclofen, paracetamol and codeine as the active ingredients.

9.

A pharmaceutical composition according to any one of the preceding claims for use in the treatment of pain.

10.

A pharmaceutical composition according to any one of claims 1 to 8 for use in the treatment of pain associated with ischaemia.

11.

A pharmaceutical composition according to any one of claims 1 to 8 for use in the treatment of skeletal muscle disorders.

12.

A pharmaceutical composition according to any one of claims 1 to 8 for use in the treatment of muscle pain.

13.

A pharmaceutical composition according to any one of claims 1 to 8 for use in the treatment of muscle pain resulting from spasticity or trauma.

14.

Use of a combination of:

a skeletal muscle relaxant;

a non-steroidal anti-inflammatory agent selected from propionic acid derivatives, acetic acid derivatives, fenamic acid derivatives, biphenylcarboxylic acid derivatives, oxicams and pharmaceutically acceptable salts thereof; and

an analgesic,

in the manufacture of a medicament for the treatment of pain.

15.

Use according to claim 14 wherein the pain is associated with ischaemia.

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16.

Use of a combination of:

a skeletal muscle relaxant;

a non-steroidal anti-inflammatory agent selected from propionic acid derivatives, acetic acid derivatives, fenamic acid derivatives, biphenylcarboxylic acid derivatives, oxicams and pharmaceutically acceptable salts thereof; and

an analgesic,

in the manufacture of a medicament for the treatment of skeletal muscle disorders in mammals.

17.

Use according to claim 16 wherein the skeletal muscle disorder is muscle pain.

18.

Use according to the preceding claim wherein the muscle pain is one resulting from spasticity or trauma.

19.

A method of treatment of a mammal suffering from pain comprising administering to the mammal a pharmaceutical composition according to any one of claims 1 to 8.

20.

A method according to claim 19 wherein the pain is associated with ischaemia.

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Fig 1

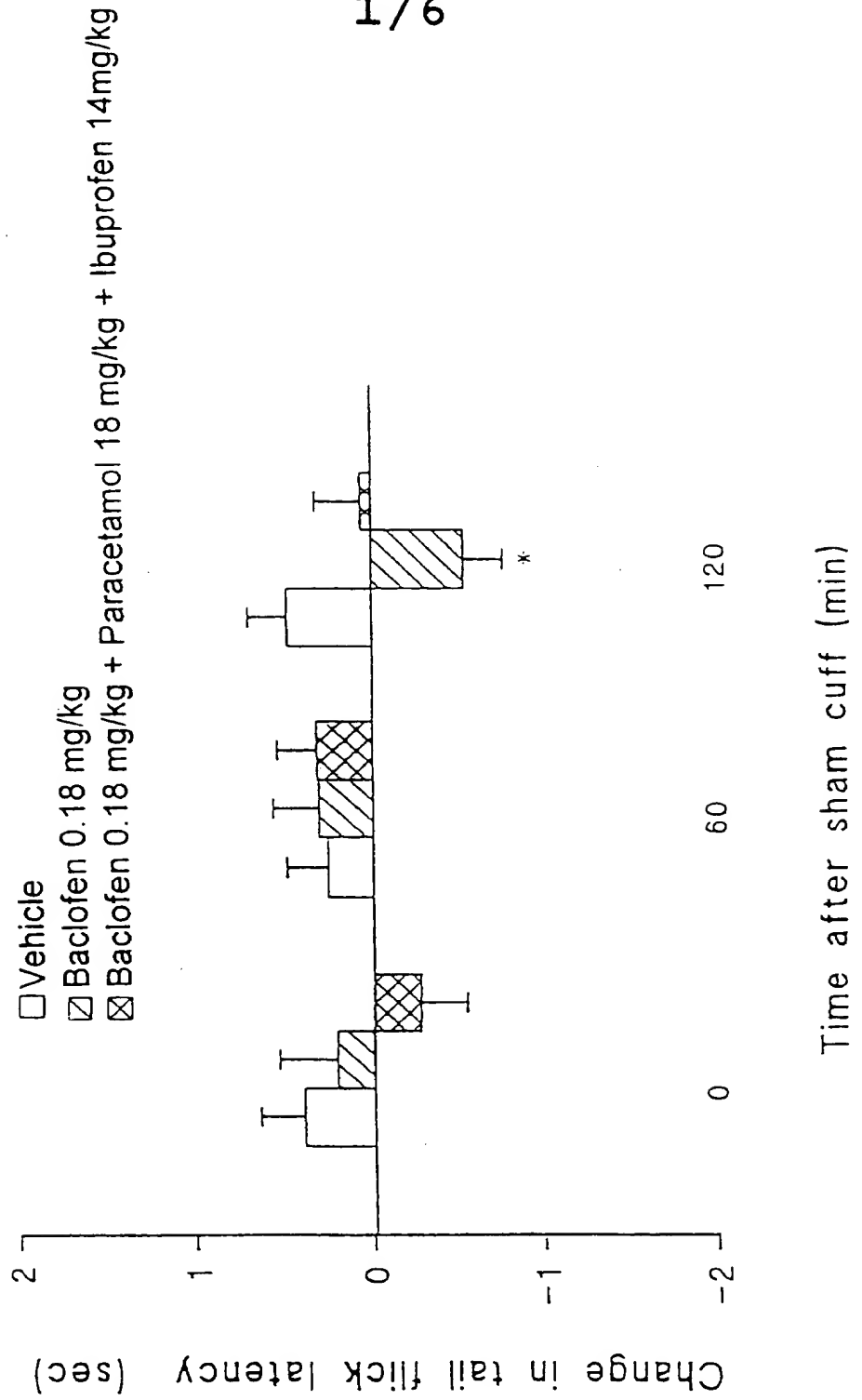
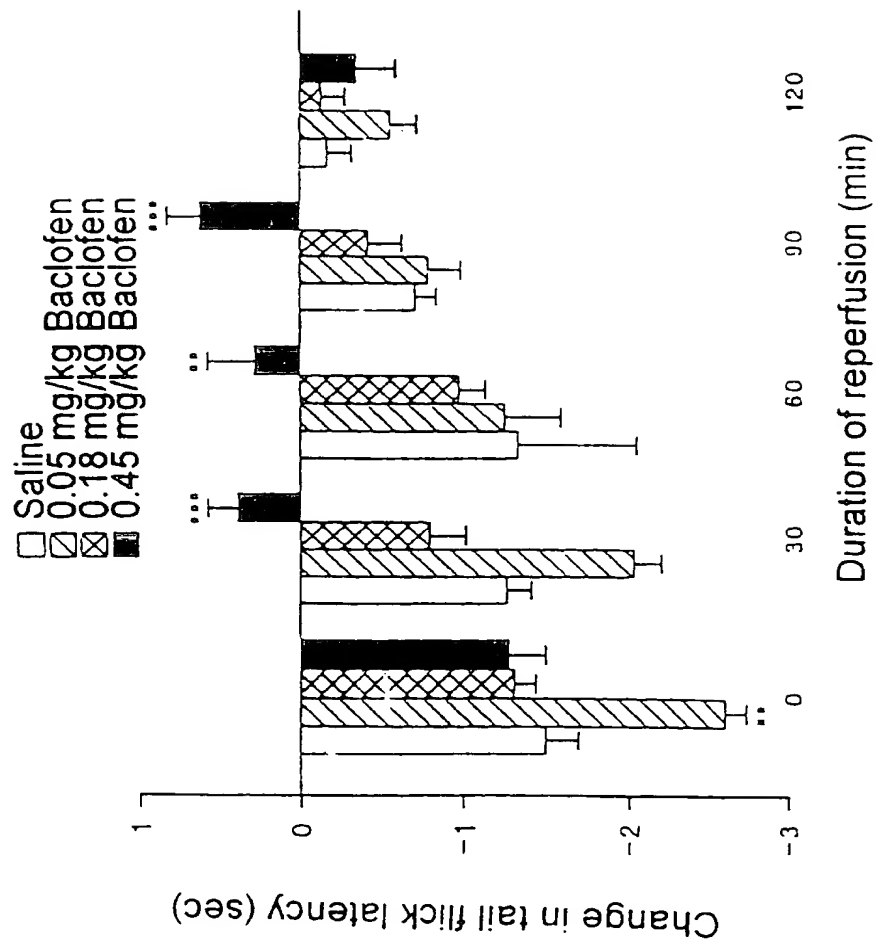


Fig 2



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~~FIG 3~~

Baclofen

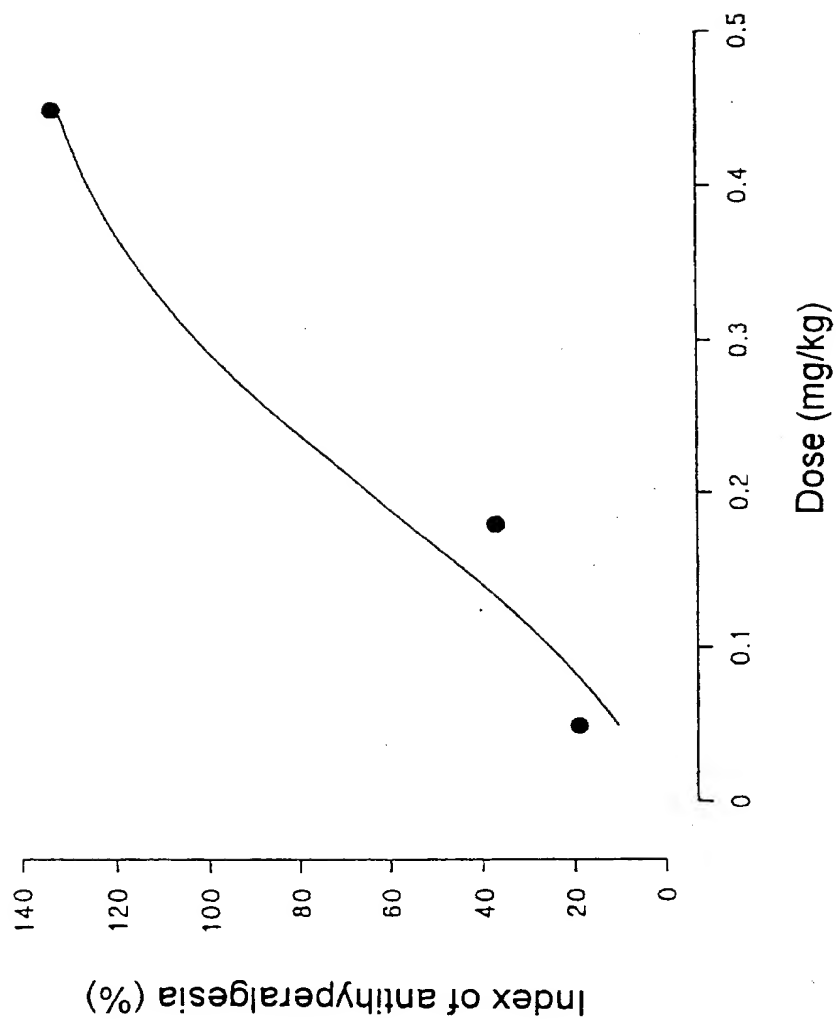
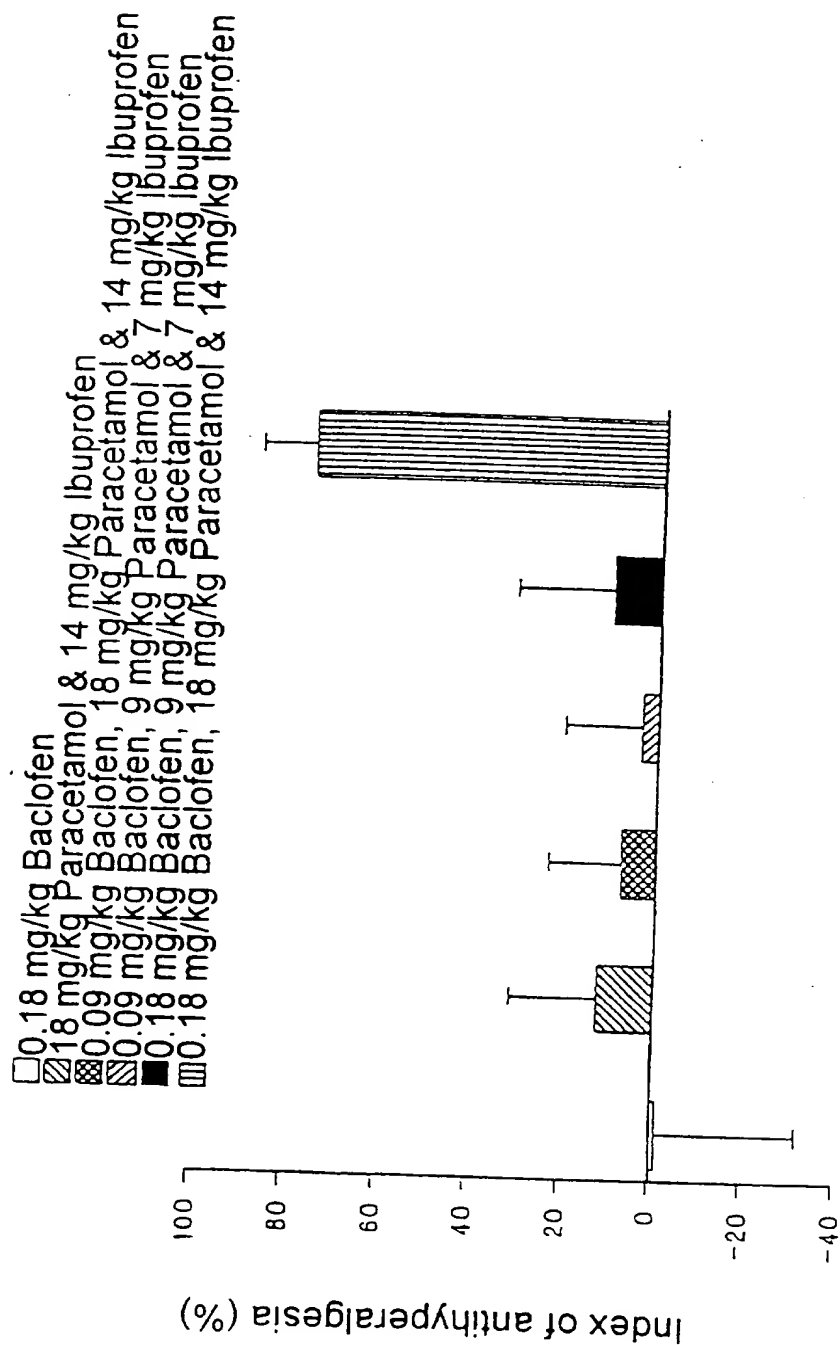
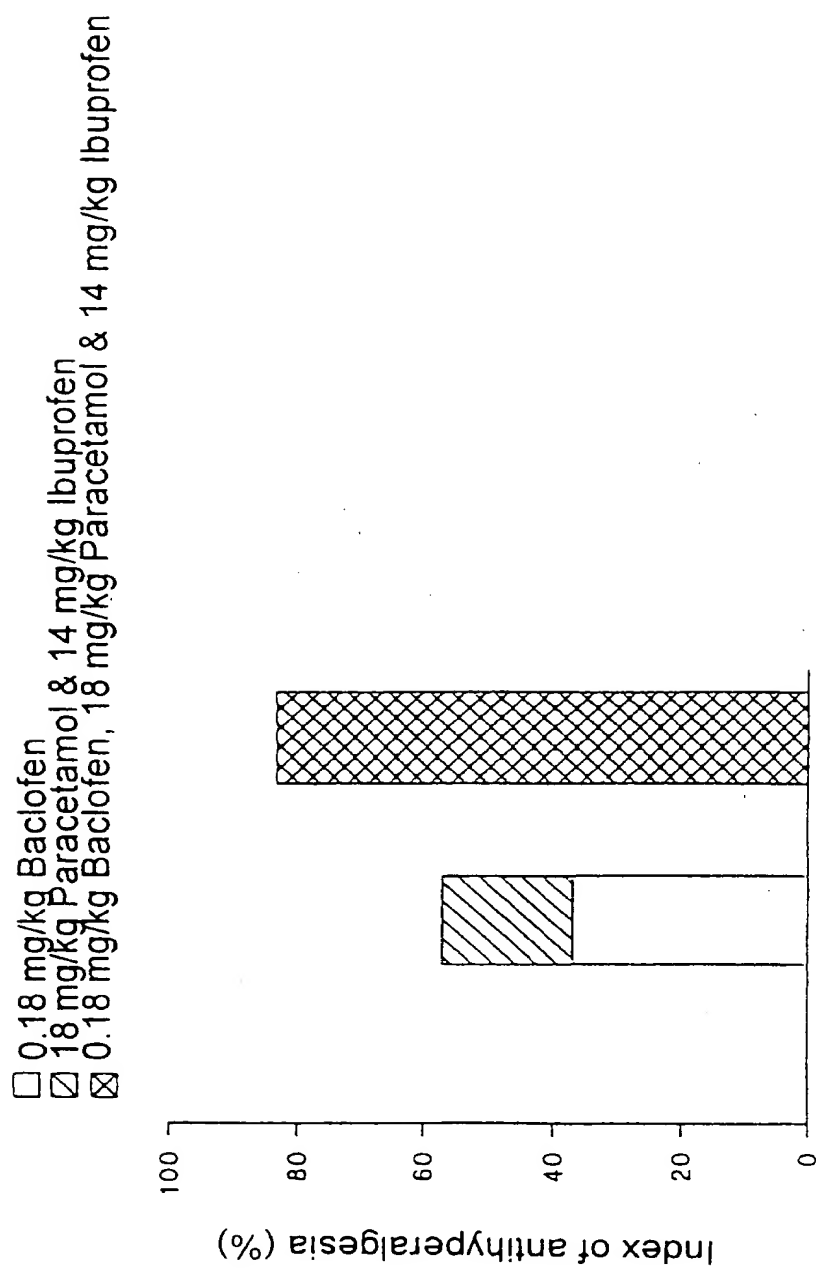


Fig 4



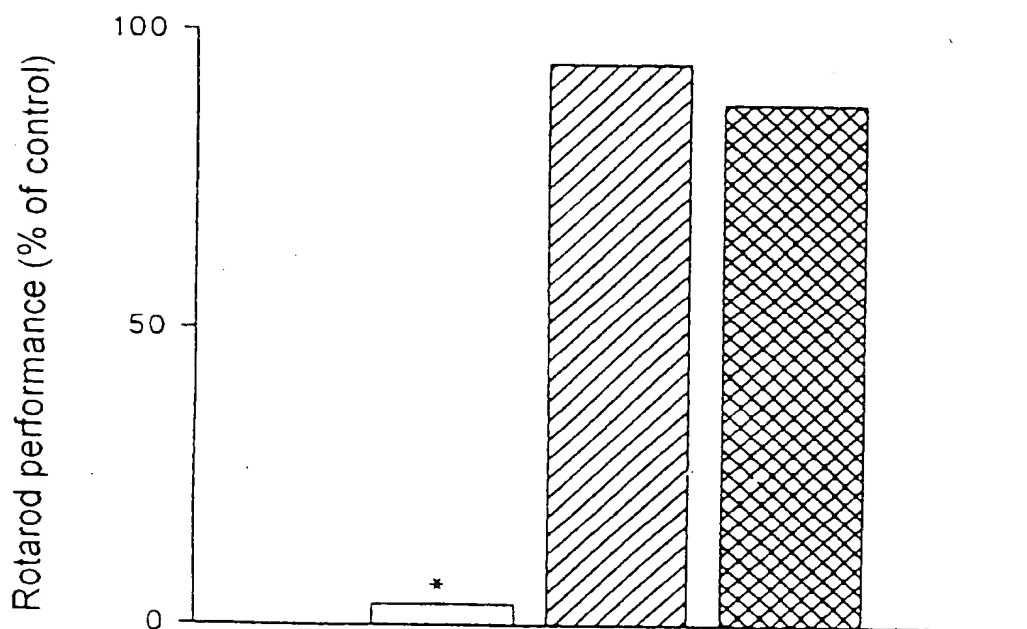
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Figure 5

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Fig 6

- ☐ Baclofen 0.45 mg/kg
- ☒ Baclofen 0.18 mg/kg
- ☒ Baclofen 0.18 mg/kg + Paracetamol 18 mg/kg
+ Ibuprofen 14 mg/kg



INTERNATIONAL SEARCH REPORT

Int. l. Application No
PCT/GB 95/02843

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/00 A61K31/19 A61K31/195 A61K31/165 A61K31/485

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 260 337 A (ROBERT T. SIMS ET AL.) 9 November 1993	1-4,9, 11-14, 16-19
Y	see abstract see column 3, line 32 - line 37 ---	5-8,10, 15,20
X	WO 86 03681 A (SUNSHINE ET AL.) 3 July 1986	1-4,9, 11-14, 16-19
Y	cited in the application see the whole document --- -/--	5-8,10, 15,20

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

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Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.

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INTERNATIONAL SEARCH REPORT

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